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EDITORIAL

Major depressive disorder: reification and (maybe) rheostasis

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The heterogeneity of clinical syndromes subsumed by diagnostic criteria for major depressive disorder (MDD) is regarded by some as a reason to abandon or modify the criteria. However, heterogeneity may be unavoidable because of the biopsychosocial complexity of depression. MDD may be characterised by complexities that cannot be distilled down to any brief set of diagnostic criteria. Psychiatrists and psychiatric epidemiologists may need to revise their expectations of this diagnosis in order to avoid over-estimating its ability to guide the selection of treatments and prediction of prognosis. An opposing perspective is that of reification, in which the diagnosis is viewed as being more real than it really is. The concept of rheostasis may help to explain some features of this condition, such as why major depressive episodes sometimes seem understandable or even adaptive (e.g. in the context of bereavement) whereas at other times such episodes are inexplicable and maladaptive.

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In this issue of Epidemiology and Psychiatric Sciences, Lorenzo-Luaces (2015) seeks to reconcile divergent opinions about the fundamental nature of major depressive disorder (MDD). The Lorenzo-Luaces review asks a question: is MDD the 'common cold' of psychiatry or is it a highly debilitating chronic illness? The author concludes that MDD is a heterogeneous condition that can be both of these things. Several additional arguments are presented in this commentary, with the goal of augmenting this discussion. First, there is a need to differentiate major depressive episodes (MDE) from MDD in any critique of the diagnostic validity of MDD. Second, it is important to challenge the idea that threshold-setting is the logical solution to these problems. Third, while the heterogeneity of MDD is clear, what are the implications of this? Should the category be abandoned or can it be used differently? Finally, the infrequently discussed concept of rheostasis deserves mention as it offers an interesting alternative perspective on these diagnostic problems.

In a highly referenced paper, Regier *et al*. (1998) noted that some people meeting diagnostic criteria for MDE do not display characteristics usually associated with illness (e.g., a clear need for treatment). This does not necessarily mean, however, that such episodes are devoid of clinical significance. In examining longitudinal data from Canada, we found that brief and mild episodes (including subthreshold episodes, those lasting only a few weeks and those not associated with suicidal ideation or marked functional impairment) nevertheless strongly predicted the subsequent course of major depression (Patten *et al*. 2010*b*). Since MDD is characterised by episodes that may have various levels of severity and persistence, it would be a mistake to confound the characteristics of specific episodes with the broader question of the conceptual validity of MDD. As a diagnostic category, MDD would seem most useful in situations where it identifies people who, without treatment, will be at risk of experiencing recurrent severe and/or persistent episodes of depression. It does not follow that every episode they experience must be particularly severe or persistent.

While it is often asserted that the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) sets its threshold for a diagnosis of MDD too low, the problem of discerning a heterogeneous condition such as MDD from the inevitable diversity of emotional experience is not merely a question of threshold setting (Wakefield, 1992; Zimmerman *et al*. 2004). This is true irrespective of whether diagnostic thresholds are defined in terms of the number of required symptoms, symptom severity, persistence, impact of the syndrome on functioning and safety, or some combination of these factors. A higher threshold for diagnosis will predictably increase specificity at the expense of sensitivity while setting the bar lower can be expected to increase sensitivity at the cost of decreased specificity. Of course, invoking terminology such as sensitivity

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and specificity implies a gold standard. While it is true that there is currently no available gold standard instrument, there is nevertheless an unarticulated gold standard: strong predictive validity for prognosis and treatment response. The Lorenzo-Luaces review emphasises that current criteria for MDD fall short of this ideal but the author does not advocate abandonment of diagnostic criteria altogether. Indeed, to do so could reduce reliability, rob psychiatry of an empirical 'common language' and might potentially impede the translation of research evidence into clinical practice.

The Lorenzo-Luaces review ultimately concludes that more research is needed to refine this diagnosis and to better understand its implications. This is certainly true, but scientific advances of this sort are likely to be incremental and have thus far been slow in coming. Until an enhanced definition surfaces the best interim solution may actually be greater acceptance of the heterogeneity of this condition. This would involve invoking a more flexible range of clinical responses to MDD, acknowledging the limitations of its crude categorisation. As pointed out in the review, this approach demands a better evidence-base than currently exists. A goal of research should be to generate knowledge capable of guiding management, including identification of situations (falling under the broad umbrella of MDD) in which: no intervention is needed; where monitoring (such as 'watchful waiting') is helpful; when unobtrusive interventions (education, exercise) are most suitable; and when more formal treatments are needed.

The idea that MDD must or should be a real illness ('truly ill' to use the words of Lorenzo-Luaces) involves a degree of reification of the syndromal definition of MDD. Many apparently mentally healthy people experience similar syndromes in relation to major losses or threatening life events, bereavement being a classical example (Wakefield *et al*. 2007). Sensitivity to distress, ability to function in spite of symptoms and vulnerability to suicide are clinically important aspects of the syndrome of depression, but it is unrealistic to expect that a diagnostic definition could subsume all of the implications of such factors. To do so would require excessive definitional complexity; which would likely come at a cost of diminished clinical utility. MDD is inevitably intertwined with the personal and social contexts in which it occurs. The common tendency to reify this diagnosis may explain a tendency to over-estimate the extent to which it can be used as a predictor of prognosis or treatment response. This error, in turn, leads to many of the problems highlighted in the Lorenzo-Luaces review.

One of the most troubling findings in psychiatric epidemiology is the tendency for the lifetime prevalence of many of the common mental disorders, MDD included, to decline with age. Lorenzo-Luaces takes this phenomenon as an indication that 'forgotten' episodes must have been trivial ones. This is not necessarily correct. The apparent decline in recall of past episodes starts long before 'old age' with peak lifetime prevalence occurring in middle age (Patten *et al*. 2010*a*). Autobiographical memory is far from perfect. One study reported that only about half of people hospitalised for depression were able to recall their symptoms in a way that could confirm a diagnosis 25 years later (Andrews *et al*. 1999). These measurement problems do not necessarily mean that past episodes were trivial or unimportant at the time of their occurrence.

Lorenzo-Luaces adopts Regier's use of the term 'homeostatic' to describe episodes that are adaptive rather than maladaptive (Regier *et al*. 1998). The term 'allostatic' may be more appropriate since the issue is that of adaptation to an external environment rather than maintenance of internal balance (McEwen, 2003). The term 'rheostasis' may be even more fitting since depressive disorders may reflect problems with calibration of otherwise adaptive mechanisms. A potential example may be found in Meaney's work on epigenetic programming of stress responses (Meaney *et al*. 2007). Epigenetic regulation may be an example of a strategy for calibrating stress responses to environmental conditions. Nesse (2005) has pointed out that evolutionarily adaptive rheostatic mechanisms can produce false positive 'all or nothing reactions' (both depression and panic attacks may be examples) while reacting to an environment that contains both signal and noise (Nesse, 2005). Nesse's ideas provide an interesting contrast to discussions of sensitivity and specificity, e.g. of DSM-5 criteria as in the third paragraph of this commentary. These ideas posit that sensitivity and specificity are parameters quantifying ways in which the brain itself responds to its environment. Rather than a dichotomy between adaptive and maladaptive types of depression, this framework suggests that a depressive episode might be a true positive (a 'hit'), a false positive (false alarm), true negative or false negative. According to Nesse (2005), even an optimally calibrated system can produce false alarms, a so-called 'fire alarm effect.' Through the lens of rheostasis, strong clinical evidence of psychopathology is more likely to be found in maladaptive patterns of symptoms and episodes over time rather than by examination of the clinical characteristics of specific episodes, or refined definitions of such episodes. DSM-5, unfortunately, does not support such an approach since even a single MDE can support a diagnosis of MDD.

Lorenzo-Luaces asserts that most episodes of major depression are brief, a statement supported by

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epidemiological data. However, this statement deserves further epidemiological refinement. Most new-onset episodes are brief but, since prevalence is proportional to incidence and duration, longer-lasting episodes accumulate in the population, such that the assertion has more veracity when it is applied to incident cases in the community than cases presenting in clinical settings, for an animated depiction of this phenomenon, see additional file 2 in Patten (2006). Delays in reaching clinical services will result in selection of more persistently ill patients. The rate of recovery from MDE declines as duration of an episode increases, leading to a characteristic pattern of cumulative recovery (Vos *et al*. 2004; Patten, 2006) and secondarily to a mean duration that is typically much longer than the median duration. Also caution is needed in referring to 'placebo response rates' in an episodic condition, since regression to the mean is important too. A person experiencing recurrent episodes may have a high rate of improvement while being treated with placebo, but this does not mean that the placebo treatment caused the improvement, nor that the patient's episode was a trivial one.

MDD is best treated as a label to enhance communication and increase reliability of diagnosis. It should not be regarded as an effective direct guide for clinical action.

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